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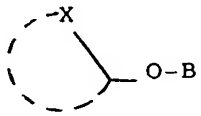
EP 0 306 148 B1

Description

This invention relates to ethers. In particular the invention relates to novel ethers, to processes for their preparation, their use and to pharmaceutical compositions containing them. The ethers are useful as antagonists of specific 5-hydroxytryptamine (5-HT) receptors as explained hereinbelow.

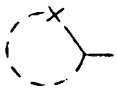
The novel ethers of the present invention are compounds of the general formula (I)



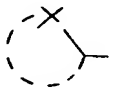
(I)

the heteroaromatic N-oxides of the compounds in which X is nitrogen; and the pharmaceutically acceptable acid addition salts of the compounds of formula I or the N-oxides, wherein

represents a heteroaryl group containing at least one hetero atom X selected from the group consisting of nitrogen, oxygen and sulphur and being optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di(C_{1-4}-alkylamino), halogen, trifluoromethyl, phenyl, halophenyl, C_{1-4}-alkylphenyl, C_{1-4}-alkoxyphenyl, carboxy, carboxamido, nitro, thiol, C_{1-4}-alkylthio and C_{1-4}-alkoxycarbonyl; -B represents a saturated azabicyclic ring comprising from 7 to 11 ring carbon atoms and a ring nitrogen atom which is separated from the O atom of the ether linkage by 2 or 3 ring carbon atoms and where the ring nitrogen atom is not in the bridgehead position the N may be unsubstituted or substituted by a group R^1 where R^1 is C_{1-6}-alkyl, C_{3-5}-alkenyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-, C_{1-2}alkyl or aryl- or heteroaryl-C_{1-2}-alkyl (where the aryl group is a phenyl or naphthyl radical optionally substituted by one or more halogen, C_{1-4}-alkoxy or C_{1-4}-alkyl groups and the heteroaryl group is a mono- or bicyclic heteroaryl radical containing one or two hetero atoms selected from oxygen, nitrogen and sulphur); and the -OB moiety is ortho to the hetero atom X; with the proviso that

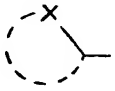


is other than a substituted or unsubstituted isoquinolinyl radical and that when B represents a quinuclidyl or a tropanyl radical,

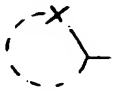


is other than a substituted or unsubstituted 2-pyridyl radical.

Compounds of formula I in which

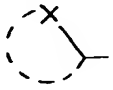


represents 2-pyridyl optionally substituted by specified substituents and B represents a quinuclidyl or tropanyl radical are disclosed generically, and compounds in which



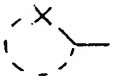
represents 6-chloropyrid-2-yl- and B represents tropan-3-yl or quinuclidyl are disclosed specifically, in GB 2152048A. The compounds are stated to have analgesic activity. The publication does not disclose 5-HT_3-antagonistic activity for the compounds. The compounds are excluded from the above scope.

Examples of heterocycles from which the heteroaryl radical



is derived include 5 membered heterocycles with one hetero atom (eg furan, pyrrole and thiophene) which may be ring fused to, for example, a benzene or cyclohexane ring (eg benzo(b)furan, benzo(c)furan, indole, benzothiophene); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3-positions which may be ring fused to other rings (eg oxazoles, pyrazoles, imidazoles, thiazoles, benzimidazoles, benzoxazoles, purines); 5-membered heterocycles with three heteroatoms which may be ring fused to other rings (eg triazoles, benzotriazoles, oxadiazoles); 6-membered heterocycles with one heteroatom and which may be ring fused to other rings (eg pyridine, quinoline, phenanthrine, 5,6-cycloheptenopyridine, 5,6-cyclohexenopyridine); 6-membered heterocycles with two heteroaatoms which may be ring fused to other rings (eg pyridazines, cinnolines, phthalazines, pyrazines, quinoxalines, pyrimidines, quinazolines); 6-membered heterocycles with three heteroatoms (eg 1,3,5-triazine) 7-membered heterocycles which may be fused to to other rings (eg diazepines, benzodiazepines). In each example the heterocycles may optionally be substituted by C_{1-4}alkyl, C_{1-4}alkoxy, amino,
C_{1-4}alkylamino, di(C_{1-4}-alkyl)amino, halogen (preferably fluorine or chlorine), trifluoromethyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4}-alkoxy phenyl, carboxy, carboxamido, nitro, thiol, C_{1-4}-alkylthio, C_{1-4}-alkoxycarbonyl.

Preferred

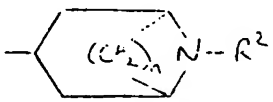


groups include 2-pyridyl optionally substituted by, for example, chloro, nitro, C_{1-4}-alkyl or carboxamido; 2- or 4- pyrimidyl optionally substituted by for example chloro, amino, C_{1-4}-alkoxy; 2-pyrazinyl optionally substituted by, for example, halo or C_{1-4}-alkyl; 2-pyridazinyl optionally substituted by, for example, halo or C_{1-4}-alkoxy; 2-quinolyl optionally substituted by
C_{1-4}-alkyl; 2-thienyl; 2-benzo(b)thienyl; 1H-indazol-3-yl optionally substituted by, for example, nitro or C_{1-4}-alkyl; 2-benzoxazolyl; 2-benzothiazolyl; and 6-phenanthrinyl.

Particularly preferred groups are optionally substituted pyridazines and also the bicyclic groups specifically mentioned above.

Examples of the saturated azabicyclic ring B include groups of the following formulae

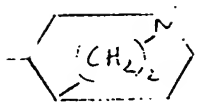
(a)



(II)

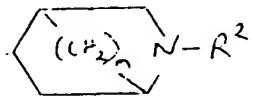
where n is 2,3 or 4 and R^2 is hydrogen or has the meaning given for R^1 above

(b)



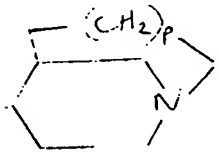
(III)

(c)



(IV)

where R^2 has the meaning given above and m is 1, 2 or 3 and
(d)



(V)

where p is 0, 1 or 2.

The preferred group B is that of formula (II) particularly that in which n is 2 and that in which R^2 is C_{1-4}-alkyl, preferably methyl. The radical in which n is 2 and R^2 is methyl is known as tropan-3-yl.

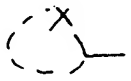
The radical of formula (III) is known as quinuclidyl.

In the radical of formula (IV), preferably m is 2, and R^2 is preferably C_{1-4}-alkyl, particularly methyl.

In the radical of formula (V), p is preferably 1.

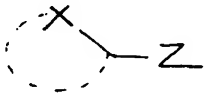
The groups of formulae (II) to (IV) may contain at least one asymmetric carbon atom so that the compounds of the invention can exist in different stereoisomeric forms. The compounds can, for example, exist as racemates or optically active forms. Furthermore radicals such as those of formulae (II) to (IV) can exist in two different configurations corresponding to the endo configuration as in tropine and the exo configuration as in pseudotropine. The endo configuration is preferred.

In the compounds of formula I, any alkyl group is preferably methyl, ethyl, propyl or butyl; any alkoxy group is preferably methoxy, ethoxy or propoxy; an alkenyl group is preferably allyl or methallyl; a cycloalkyl is preferably cyclopentyl or cyclohexyl; cycloalkyl-alkyl is preferably cyclopentylmethyl or cyclohexylmethyl; arylalkyl is preferably benzyl; and where the R^1 group contains a heteroaryl radical this may be any one of the heteroaryl groups mentioned above in connection with the



radical.

The compounds of the invention may be prepared by methods known for the preparation of ethers. For example, a compound of formula

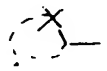


(VI)

or a N-oxide thereof may be condensed with a compound of formula

Z^1-B (VII)

where



and B are as defined above and one of Z and Z^1 is hydroxy and the other is a leaving group such as halogen, C_{1-6}-alkylsulphonyloxy (eg methylsulphonyloxy) or arylsulphonyloxy where the aryl radical may be, for example, phenyl or naphthyl optionally substituted by C_{1-4}-alkyl (eg p-toluenesulphonyloxy). Preferably Z is a leaving group, particularly halogen, and Z^1 is hydroxy. The condensation may be carried out in presence of a condensing agent, particularly a basic condensing agent such as an alkali metal or alkaline earth metal hydroxide or carbonate, potassium or sodium hydride, phenyl- or an alkyl-lithium (eg butyllithium), an alkali metal amide (eg lithium diisopropylamide) or an organic base such as a tertiary amine, pyridine or piperidine. The condensation may be carried out in an organic solvent. The anion of the alcohol may be first prepared by reaction of the alcohol with a strong base and the anion may be subsequently be reacted with the second reactant containing the leaving group.

It will be realised that if either the reactant (VI) or (VII) contains groups that would be affected under the reaction conditions employed for the condensation reaction the group may be protected and the protecting group subsequently removed. For example hydroxy groups may be protected by formation of acetals or ethers (eg benzyl or silyl ethers) and amino groups may be protected by formation of urethanes or N-benzyl derivatives.

In addition, any substituent present in the final compound of formula (I) may be removed or replaced by another substituent using methods that are known in the art. For example a chloro substituent on the heteroaromatic ring may be removed by catalytic hydrogenation or an alkoxycarbonyl substituent may be reduced to hydroxymethyl.

The compounds of formula (I) in which X is nitrogen may be converted into their heteroaromatic N-oxides by methods known for analogous compounds. For example, the compounds of formula (I) may be oxidised eg in an inert solvent with a peracid (eg peracetic acid, perbenzoic acid or m-chloroperbenzic acid), hydrogen peroxide, an alkali metal peroxide or an alkyl peroxide. Oxidation may give the di-oxide which may be subsequently reduced, eg with sulphur di-oxide, to the mono N-oxide of the nitrogen containing heteroaromatic ring.

The starting materials of formulae (VI) and (VII) are described in the literature or may be prepared by methods known for analogous compounds.

If in the processes described above the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compound.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic and p-toluenesulphonic acids. The compounds of the present invention possess pharmacological activity. In particular they antagonise specific 5-hydroxytryptamine (5-HT) receptors in warm blooded animals. Specifically the compounds possess 5-HT_3 antagonistic activity and hence are of value in conditions where antagonism of 5-HT_3 receptors is desirable. 5-HT_3-antagonists are also termed "antagonists of "neuronal" 5-hydroxytryptamine receptors" and "serotonin (5-hydroxytryptamine) M-receptor antagonists". Such compounds have been described as being useful inter alia in the treatment of migraine, emesis, anxiety, gastrointestinal disorders and as anti-psychotics.

The compound of the invention are tested for 5-HT_3 receptor antagonism in the isolated vagus nerve of the rat by a method based upon that of Ireland S.J. and Tyers M.B., Brit. J. Pharmacol., 1987, 90, 229-238. The procedure relies upon the ability of 5-HT to induce depolarization of neurones in the cervical vagus nerve by a direct action on 5-HT_3 receptors. A concentration-response curve to 5-HT induced depolarization is obtained and the antagonists are added to the bath containing the isolated nerve before repeating the 5-HT concentration-response curve. Antagonist potency is estimated for the 5-HT concentration ratios and expressed as an apparent pK_B value (where K_B is the antagonist dissociation constant). When tested by this

procedure endo-8-methyl-3-(2-quinolyloxy)-8-azabicyclo[3.2.1]octane, a representative compound of this invention, had a pK_B of 7.5.

The compounds of the invention are also tested for 5-HT_3 antagonistic activity in the isolated right atrium of the rabbit heart based upon the method of Fozard J.R., Naunyn-Schmiedeberg's Arch. Pharmacol., 1984, 326, 36-44. This procedure relies upon the ability of 5-HT to stimulate 5-HT_3 receptors present on sympathetic nerve terminals in the heart, causing release of noradrenaline which evokes an increase in the spontaneous rate of beating. The antagonist potency is expressed in a similar manner to that of the preceding test method ie as an apparent pK_B. When tested by this procedure endo-8-methyl-3-(2-quinolyloxy)-8-azabicyclo[3.2.1]octane, a representative compound of this invention, had a pK_B of 8.6.

The invention further provides a compound of formula (I) or its heteroaromatic N-oxide or a pharmaceutically acceptable acid addition salt thereof for use in antagonising 5-HT_3 receptors in a mammal.

The invention also provides a pharmaceutical composition comprising a compound of the invention in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid and a liquid.

Solid form compositions include powders, granules, tablets, capsules (eg hard and soft gelatin capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aids binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, eg from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solibilizers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above eg cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols eg glycerol and glycols) and their derivatives, and oils (eg fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

The compounds of the invention can also be administered by the nasal route. When formulated for nasal administration the compositions may comprise a compound of the invention in a liquid carrier; such compositions may be administered for example in the form of a spray or as drops. The liquid carrier may be water (which may contain further components to provide the desired isotonicity and viscosity of the composition). The composition may also contain additional excipients such as preservatives, surface-active agents and the like. The compositions may be contained in a nasal applicator that enables the composition to be administered as drops or as a spray. For administration from an aerosol container the composition should also include a propellant.

Preferably the pharmaceutical composition is in unit dosage form, eg as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in packaged form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750

mg or more, according to the particular need and the activity of the active ingredient.

The following Examples illustrate the invention:

Example 1

Endo-8-methyl-3-(2-pyrimidyloxy)-8-azabicyclo[3.2.1]octane

A stirred solution of tropine (6 g, 42.5 mmol) in dry dimethyl sulphoxide (50 ml) was treated with sodium hydride, 50% dispersion in oil (2.3 g containing ca. 47.9 mmol sodium hydride) under nitrogen. After 30 min, the solution was treated with 2-chloropyrimidine (5.2 g, 45.4 mmol), and after 3 h treated with water (200 ml) and extracted with ethyl acetate (2 x 100 ml). The organic phases were combined and extracted with 0.25 N-HCl (200 ml). The aqueous extract was washed with ethyl acetate (2 x 200 ml), basified with sodium hydroxide and extracted with ethyl acetate (2 x 200ml). The extracts were dried (magnesium sulphate) and evaporated in vacuo to give a yellow liquid. The liquid was converted into the hydrochloride salt with ethereal hydrogen chloride and methanol. The salt was recrystallised from ethyl acetate-methanol to give the title compound as the dihydrochloride (3.86 g), mp 205-207° (dec.)
(Found: C,48.5; H,6.7; N,14.1 $C_{12}H_{17}N_3O.2HCl$ requires C,48.6; H,6.8; N,14.2%).

Example 2

Endo-8-methyl-3-(2-quinolyloxy)-8-aza-bicyclo[3.2.1]octane

A stirred solution of tropine (5.94g, 42.1 mmol) in dry dimethyl sulphoxide (40 ml) was treated with sodium hydride, 50% dispersion in oil (2.3g containing ca. 47.9 mmol sodium hydride) under nitrogen. After 30 min the solution was treated with 2-chloroquinoline (6.88 g, 42.1 mmol), and after 3 h treated with water (200 ml). The solution was extracted with ether (3 x 150 ml). The extracts were combined and extracted with 0.25 N-HCl (200 ml). The aqueous extract was washed with ether (200 ml), basified with 10 N-NaOH, and extracted with ethyl acetate (2 x 200 ml). The extracts were dried (magnesium sulphate) and evaporated in vacuo to give a yellow solid which was triturated with ether (10 ml). The solid was converted into the hydrochloride salt with ethereal hydrogen chloride and methanol. The salt was recrystallised from ethyl acetate-methanol to give the title compound as the dihydrochloride (4.1 g), m.p. 190-200° (dec) .
Found: C,59.3; H,6.7; N,7.85. $C_{17}H_{20}N_2O$. 2HCl requires C,59.8; H,6.5; N,8.2%).

Example 3

Endo-8-methyl-3-(2-pyrazinyloxy)-8-azabicyclo[3.2.1]octane

The above compound was prepared from tropine (9.09 g, 63.7 mmol), 2-chloropyrazine (7.33 g, 64.0 mmol), and sodium hydride, 50% dispersion in oil (3.4 g) using the method described in Example 1.

The dihydrochloride salt was isolated as colourless crystals (8.75 g), m.p. 244-246° (dec) (from methanol-ethyl acetate)
(Found: C,47.1; H,6.7; N,13.7. $C_{12}H_{17}N_3O$ 2HCl.
$\frac{3}{4}H_2O$ requires C,47.2; H,6.8; N,13.8%).

Example 4

Endo-3-(6-chloropyridazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

The above compound was prepared by the method described in Example 1.

The reaction of tropine (6.0 g, 42.6 mmol), 3,6-dichloropyridazine (12.7 g, 85.2 mmol), and sodium hydride, 50% dispersion in oil (2.25 g) gave a brown solid which was purified by chromatography (alumina; ether).

The dihydrochlorise salt was isolated as colourless crystals (0.8 g), m.p. 181-184° (dec.) (from methanol-ethyl acetate)
(Found: C,43.5; H,5.6; N, 13.1. $C_{12}H_{16}ClN_3O$. 2HCl.
$\frac{1}{4}H_2O$ requires C,43.5; H,5.6; N,12.7%).

Example 5

Endo-3-(6-chloropyrazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

The compound was prepared from 2,6-dichloropyrazine (6.49 g, 43.6 mmol), tropine (5.58 g, 39.6 mmol) and sodium hydride, 50% dispersion in oil (2.1 g) by the method outlined in Example 1.

The product was converted to the hydrochloride salt and recrystallised from methanol-ethyl acetate to give the title compound as the hydrochloride (3.77 g), m.p. 275-277° (dec.)

(Found: C,49.7; H,5.8; N,14.6.

$C_{12}H_{16}ClN_3O$. HCl required C,49.6; H,5.9; N,14.5%).

Example 6

Endo-3-(benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

A stirred solution of tropine (6.10g, 43.3mmol) in dry dimethylsulphoxide (100ml) was treated with sodium hydride, 50% dispersion in oil (2.3g) under nitrogen. After 40 min, 2-chlorobenzothiazole (6.2ml, 47.7mmol) was added and, after 18h, the mixture was poured into water (400ml). The precipitate was filtered and recrystallised from ethyl acetate to give the title compound as yellow crystals.

The hydrochloride salt was isolated from ethyl acetate-methanol as white crystals (7.04g) m.p. 225 - 227°- (dec.).

(Found: C,58.2; H,6.2; N,9.0. $C_{15}H_{18}N_2OS$.HCl requires C,58.0; H,6.2; N,9.0%).

Example 7

Endo-3-(pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

A solution of endo-3-(6-chloropyridazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane dihydrobromide (2.97 g, 7.3 mmol) in ethanol (250 ml) was treated with 33% w/w aqueous ammonia (50 ml), reduced with hydrogen at 50 p.s.i. using 10% palladium on charcoal (1.8 g) as catalyst, filtered, and evaporated in vacuo to dryness. The residue was azeotroped in vacuo with toluene (100 ml) and triturated with dichloromethane (200 ml). The triturates were dried ($MgSO_4$) and evaporated in vacuo to give a solid which was recrystallised from ethyl acetate - ethanol to give colourless crystals of the product (1.07 g).

The monohydrobromide salt of the product was prepared as colourless crystals, m.p. 223-227°

(Found: C,47.6; H,6.1; N,13.8

$C_{12}H_{17}N_3O$. HBI requires C,48.0; H,6.0; N,14.0%).

Example 8

2-Quinolinyl 3-quinuclidinyl ether

Sodium hydride, 80% dispersion in oil (1.11 g) was treated with dimethyl sulphoxide (100 ml) with stirring and iced water - bath cooling under a bubbler air-lock. 3-Quinuclodinol (4.227 g, 33.6 mmol) was added after 15 min and 2-chloroquinoline (6.05 g, 37.0 mmol) added after 45 min. The mixture was allowed to warm to room temperature and after 6 days poured into water (400 ml). The mixture was extracted with ethyl acetate (3 x 200 ml). The extracts were combined and extracted with 0.4 N-HCl (250 ml). The aqueous extract was washed with ethyl acetate (200 ml), basified with 2N-NaOH, and extracted with chloroform (3 x 200 ml). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give a solid which was recrystallised from methanol-ethyl acetate to yield the product free base (3.14 g)

The dihydrochloride salt of the product was prepared in methanol with etheral hydrogen chloride as colourless crystals.

(Found: C,51.55; H,6.6; N,7.2

$C_{15}H_{18}N_2O.2HCl.\ 2.5H_20$ requires C,51.6; H,6.8; N,7.5%).

Example 9

Endo-(phenanthrin-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

The title compound was prepared by the procedure given in Example 8 using 6-chlorophenanthrine (4.63g, 21.7 mmol), tropine (2.78g, 19.7 mmol), and sodium hydride, 80% dispersion in oil (0.65g, 21.7 mmol) in dimethyl sulphoxide (100ml). The crude product was purified by chromatography (alumina; ether). The dihydrochloride salt was prepared with ethereal hydrogen chloride and methanol as pale yellow crystals (2.55g),m.p. 215-235° (dec)
(Found: C, 62.3; H, 6.45; N, 6.8
$C_{21}H_{22}N_2O2HCl$ ¾ H_2O requires
C, 62.3; H, 6.35; N,6.9%).

Example 10

Endo-3-(benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane

A stirred solution of tropine (3.02g, 21.4 mmol) in dry tetrahydrofuran (40 ml) was treated dropwise with 1.48M-butyllithium in hexane (14.5ml) under an atmosphere of nitrogen. After the slight exotherm had subsided, 2-chlorobenzoxazole (2.5ml, 21.9 mmol) was added dropwise so that the temperature remained below 30°. After 1h, the solution was evaporated in vaccuo and the residue treated with chloroform (150ml). The mixture was filtered and the filtrate evaporated in vacuo to give a yellow oil. The oil was purified by chromatography (alumina;ether) to give the product as colourless crystals (4.00g) m.p. 85-87°
(Found: C, 69.5; H.7.1; N, 10.9. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H.7.0; N, 10.8%)

Example 11

Endo-18-methyl-3-(3-methyl-5,6-cyclohexenopyridin-2-yloxy)-8-azabicyclo[3.2.1]octane

This compound was prepared by the procedure given in Example 8 using 2-bromo-3-methyl-5,6-cyclohexenopyridine (8.36g, 37 mmol), tropine (4.75g, 33.6 mmol), and sodium hydride, 80% dispersion in oil (1.11g, 37 mmol) in dimethyl sulphoxide (100 ml). The crude product was purified by chromatography (alumina; di-iso-propyl ether) to give the product as a light yellow solid (0.97g,) m.p. 51-57°.

Example 12

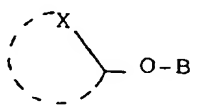
Endo-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cycloheptenopyridine-3-carboxylic acid ethyl ester

This compound was prepared by the procedure given in Example 8 using 2-bromo-5,6-cycloheptenopyridine-3-carboxylic acid ethyl ester (9.93 g, 33.3 mmol), tropine (4.28g, 30.3 mmol), and sodium hydride, 80% dispersion in oil (1g, 33.3 mmol) in dimethyl sulphoxide (100 ml). The crude product was purified by chromatography (alumina; ether) to give a colourless oil. The monohydrochloride salt of the product was prepared in methanol with ethereal hydrogen chloride and recrystallised from propan-2-ol- to give white crystals (0.59g), m.p. 234-239° (dec).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

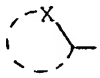
1. A compound of general formula (I)



(I)

wherein

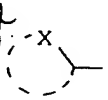
represents a heteroaryl group containing at least one hetero atom X selected from the group consisting of nitrogen, oxygen and sulphur; and being optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di(C_{1-4}-alkylamino), halogen, trifluoromethyl, phenyl, halophenyl, C_{1-4}-alkylphenyl, C_{1-4}-alkoxyphenyl, carboxy, carboxamido, nitro, thiol, C_{1-4}-alkylthio and C_{1-4}-alkoxycarbonyl; -B represents a saturated azabicyclic ring comprising from 7 to 11 ring carbon atoms and a ring nitrogen atom which is separated from the O atom of the ether linkage by 2 or 3 ring carbon atoms and where the ring nitrogen atom is not in the bridgehead position the N may be unsubstituted or substituted by a group R^1 where R^1 is C_{1-6}-alkyl, C_{3-5}-alkenyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-2}-alkyl or aryl- or heteroaryl-C_{1-2}-alkyl (where the aryl group is a phenyl or naphthyl radical optionally substituted by one or more halogen, C_{1-4}-alkoxy or C_{1-4}-alkyl groups and the heteroaryl group is a mono- or bicyclic heteroaryl radical containing one or two hetero atoms selected from oxygen, nitrogen and sulphur); and the -OB moiety is ortho to the hetero atom X; with the proviso that



is other than a substituted or unsubstituted isoquinolinyl radical and that when B represents a quinuclidyl or a tropanyl radical,

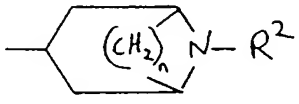
is other than a substituted or unsubstituted 2-pyridyl radical; or a heteroaromatic N-oxide of the compound in which X is nitrogen;
or a pharmaceutically acceptable acid addition salt of the compound of formula I or the N-oxide.

2. A compound as claimed in claim 1 wherein



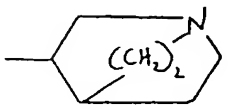
is 2-pyridyl optionally substituted by chloro, nitro, C_{1-4}-alkyl or carboxamido; 2- or 4- pyrimidyl optionally substituted by chloro, amino, C_{1-4}-alkoxy; 2-pyrazinyl optionally substituted by halo or C_{1-4}-alkyl; 2-pyridazinyl optionally substituted by halo or C_{1-4}-alkoxy; 2-quinolyl optionally substituted by C_{1-4}-alkyl; 2-thienyl; 2-benzo(b)thienyl; 1H-indazol-3-yl optionally substituted by nitro or C_{1-4}-alkyl; 2-benzoxazolyl; 2-benzothiazolyl; or 6-phenanthrinyl.

3. A compound as claimed in claim 1 or 2 wherein B is
(a)



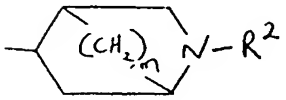
(II)

where n is 2,3 or 4 and R^2 is hydrogen or has the meaning given for R^1 in claim 1,
(b)



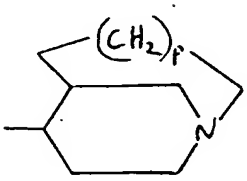
(III),

(c)



(IV)

where R^2 has the meaning given above and m is 1, 2 or 3 or
(d)



(V)

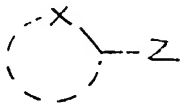
where p is 0, 1 or 2.

4. A compound as claimed in claim 3 wherein B has the formula (II) in which n is 2 and R^2 is methyl.

5. A compound as claimed in claim 1 which is endo-8-methyl-3-(2-pyrimidyloxy)-8-azabicyclo[3.2.1]octane
or
endo-8-methyl-3-(2-quinolyloxy)-8-aza-bicyclo[3.2.1]octane
or
endo-8-methyl-3-(2-pyrazinyloxy)-8-azabicyclo[3.2.1]octane
or
endo-3-(6-chloropyridazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(6-chloropyrazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
2-quinolinyl 3-quinuclidinyl ether
or
endo-(phenanthrin-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-8-methyl-3-(3-methyl-5,6-cyclohexenopyridin-2-yloxy)-8-azabicyclo[3.2.1]octane
or
endo-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cycloheptenopyridine-3-carboxylic acid ethyl ester; or a pharmaceutically acceptable salt thereof.

6. A method for the preparation of a compound claimed in claim 1 which comprises

(a) condensing a compound of formula

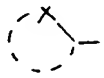


(VI)

or an N-oxide thereof, with a compound of formula

Z^1-B (VII)

where



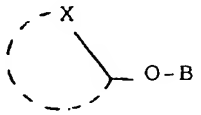
and B are as defined in claim 1 and one of Z and Z^1 is hydroxy and the other is a leaving group or
(b) replacing or removing a substituent on the heteroaryl group or the azabicyclic ring of a compound of formula (I) by methods known in the art to give another compound of formula I or
(c) oxidising a compound of formula (I) to the heteroaromatic N-oxide thereof or
(d) converting a compound of formula (I) or the heteroaromatic N-oxide thereof into its pharmaceutically acceptable acid addition salt.

7. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 5 in association with a pharmaceutically acceptable carrier.

8. A compound as claimed in any one of claims 1 to 5 for use as a pharmaceutical.

Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of general formula (I)



(I)

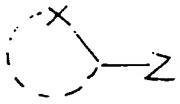
wherein

represents a heteroaryl group containing at least one hetero atom X selected from the group consisting of nitrogen, oxygen and sulphur; and being optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino, di(C_{1-4}-alkylamino), halogen, trifluoromethyl, phenyl, halophenyl, C_{1-4}-alkylphenyl, C_{1-4}-alkoxyphenyl, carboxy, carboxamido, nitro, thiol, C_{1-4}-alkylthio and C_{1-4}-alkoxycarbonyl; -B represents a saturated azabicyclic ring comprising from 7 to 11 ring carbon atoms and a ring nitrogen atom which is separated from the O atom of the ether linkage by 2 or 3 ring carbon atoms and where the ring nitrogen atom is not in the bridgehead position the N may be unsubstituted or substituted by a group R^1 where R^1 is C_{1-6}-alkyl, C_{3-5}-alkenyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-2}-alkyl or aryl- or heteroaryl-C_{1-2}-alkyl (where the aryl group is a phenyl or naphthyl radical optionally substituted by one or more halogen, C_{1-4}-alkoxy or C_{1-4}-alkyl groups and the heteroaryl group is a mono- or bicyclic heteroaryl radical containing one or two hetero atoms selected from oxygen, nitrogen and sulphur); and the -OB moiety is ortho to the hetero atom X; with the proviso

that

is other than a substituted or unsubstituted isoquinolinyl radical and that when B represents a quinuclidyl or a tropanyl radical,

is other than a substituted or unsubstituted 2-pyridyl radical; or a heteroaromatic N-oxide of the compound in which X is nitrogen;
or a pharmaceutically acceptable acid addition salt of the compound of formula I or the N-oxide.
which comprises
(a) condensing a compound of formula



(VI)

or an N-oxide thereof, with a compound of formula

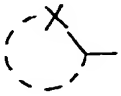
Z^1-B (VII)

where

and B are as defined above and one of Z and Z^1 is hydroxy and the other is a leaving group or
(b) replacing or removing a substituent on the heteroaryl group or the azabicyclic ring of a compound of formula (I) by methods known in the art to give another compound of formula I or
(c) oxidising a compound of formula (I) to the heteroaromatic N-oxide thereof or
(d) converting a compound of formula (I) or the heteroaromatic N-oxide thereof into its pharmaceutically acceptable acid addition salt.

2. A process as claimed in claim 1 which comprises condensing a compound of formula (VI) in which Z is halogen with a compound of formula (VII) in which Z^1 is hydroxy.

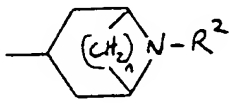
3. A process as claimed in claim 1 or 2 wherein in the product



is 2-pyridyl optionally substituted by chloro, nitro, C_{1-4}-alkyl or carboxamido; 2- or 4- pyrimidyl optionally substituted by chloro, amino, C_{1-4}-alkoxy; 2-pyrazinyl optionally, substituted by halo or C_{1-4}-alkyl; 2-pyridazinyl optionally substituted by halo or C_{1-4}-alkoxy; 2-quinolyl

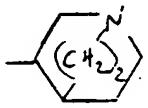
optionally substituted by C_{1-4}-alkyl; 2-thienyl; 2-benzo(b)thienyl; 1H-indazol-3-yl optionally substituted by nitro or C_{1-4}-alkyl; 2-benzoxazolyl; 2-benzothiazolyl; or 6-phenanthrinyl.

4. A process as claimed in any one of claims 1 to 3 wherein in the product B is
(a)



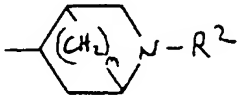
(II)

where n is 2,3 or 4 and R^2 is hydrogen or has the meaning given for R^1 in claim 1,
(b)



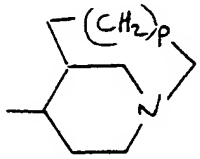
(III),

(c)



(IV)

where R^2 has the meaning given above and m is 1, 2 or 3 or
(d)



(V)

where p is 0, 1 or 2.

5. A process as claimed in claim 4 wherein B has the formula (II) in which n is 2 and R^2 is methyl.

6. A process as claimed in claim 1 wherein the product is
endo-8-methyl-3-(2-pyrimidyloxy)-8-azabicyclo[3.2.1]octane
or
endo-8-methyl-3-(2-quinolyloxy)-8-aza-bicyclo[3.2.1]octane
or
endo-8-methyl-3-(2-pyrazinyloxy)-8-azabicyclo[3.2.1]octane
or
endo-3-(6-chloropyridazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(6-chloropyrazin-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(pyridazin-3-yloxy)-8-methyl-8-azabicycloc[3.2.1]octane

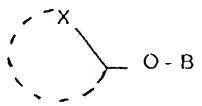
or
2-quinolinyl 3-quinuclidinyl ether
or
endo-(phenanthrin-6-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-3-(benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3.2.1]octane
or
endo-8-methyl-3-(3-methyl-5,6-cyclohexenopyridin-2-yloxy)-8-azabicyclo[3.2.1]octane
or
endo-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cycloheptenopyridine-3-carboxylic acid ethyl ester;
or a pharmaceutically acceptable salt thereof.

7. A process for preparing a pharmaceutical composition which comprises bringing a compound of general formula (I) as defined in claim 1, or a heteroaromatic N-oxide of the compound in which X is nitrogen or a pharmaceutically acceptable acid addition salt of the compound of formula (I) or the N-oxide, into association with a pharmaceutically acceptable carrier.

8. A process as claimed in claim 7 wherein the active ingredient is prepared by the process claimed in any one of claims 1 to 6.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

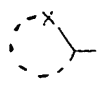
1. Verbindung der allgemeinen Formel (I)



(I),

worin

eine Heteroarylgruppe mit mindestens einem Heteroatom X ausgewählt aus der Gruppe bestehend aus Stickstoff, Sauerstoff und Schwefel und gegebenenfalls substituiert durch eine oder mehrere Gruppen ausgewählt aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, Amino, C_1-C_4-Alkylamino, Di(C_1-C_4-alkylamino), Halogen, Trifluormethyl, Phenyl, Halogenphenyl, C_1-C_4-Alkylphenyl, C_1-C_4-Alkoxyphenyl, Carboxy, Carboxamido, Nitro, Thiol, C_1-C_4-Alkylthio und C_1-C_4-Alkoxycarbonyl ist; -B einen gesättigten azabicyclischen Ring mit 7 bis 11 Ringkohlenstoffatomen und einem Ringstickstoffatom, das vom O-Atom der Etherbindung durch 2 oder 3 Ringkohlenstoffatome getrennt ist, und, wenn das Ringstickstoffatom nicht in der Brückenkopfstellung ist, das N unsubstituiert oder durch eine Gruppe R^1 substituiert sein kann, wobei R^1 C_1-C_6-Alkyl, C_3-C_5-Alkenyl, C_3-C_6-Cycloalkyl, C_3-C_6-Cycloalkyl-C_1-C_2-alkyl oder Aryl -oder Heteroaryl-C_1-C_2-alkyl ist (wobei die Arylgruppe ein Phenyl- oder Naphthylrest ist, der gegebenenfalls ein- oder mehrfach durch Halogen, C_1-C_4-Alkoxy oder C_1-C_4-Alkyl substituiert ist, und die Heteroarylgruppe ein mono- oder bicyclischer Heteroarylrest mit einem oder zwei Heteroatomen ausgewählt aus Sauerstoff, Stickstoff und Schwefel ist), und die Gruppe -OB ortho zum Heteroatom X ist; mit der Maßgabe, daß



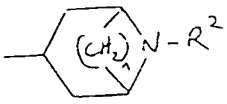
von einem substituierten oder unsubstituierten Isochinoolinylrest verschieden ist und daß, wenn B einen Chinuclidyl- oder Tropanylrest darstellt,

von einem substituierten oder unsubstituierten 2-Pyridylrest verschieden ist, oder ein heteroaromatisches N-Oxid der Verbindung, worin X Stickstoff ist, oder ein pharmazeutisch annehmbares Säureadditionssalz der Verbindung der Formel (I) oder des N-Oxids.

2. Verbindung nach Anspruch 1, worin

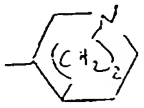
2-Pyridyl gegebenenfalls substituiert durch Chlor, Nitro, C_1-C_4-Alkyl oder Carboxamido; 2- oder 4-Pyrimidyl gegebenenfalls substituiert durch Chlor, Amino, C_1-C_4-Alkoxy; 2-Pyrazinyl gegebenenfalls substituiert durch Halogen oder C_1-C_4-Alkyl; 2-Pyridazinyl gegebenenfalls substituiert durch Halogen oder C_1-C_4-Alkoxy; 2-Chinolyl gegebenenfalls substituiert durch C_1-C_4-Alkyl; 2-Thienyl; 2-Benzo(b)-thienyl; 1H-Indazol-3-yl gegebenenfalls substituiert durch Nitro oder C_1-C_4-Alkyl; 2-Benzoxazolyl; 2-Benzothiazolyl oder 6-Phenanthrinyl ist.

3. Verbindung nach Anspruch 1 oder 2, worin B
(a)



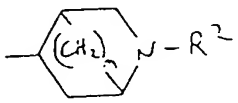
(II),

worin n 2, 3 oder 4 ist und R^2 Wasserstoff ist oder die für R^1 in Anspruch 1 angegebene Bedeutung hat,
(b)



(III),

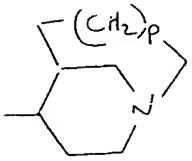
(c)



(IV),

worin R^2 die oben angegebene Bedeutung hat und m 1, 2 oder 3 ist, oder

(d)



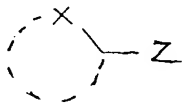
(V),

worin p Null, 1 oder 2 ist, darstellt.

4. Verbindung nach Anspruch 3, worin B die Formel (II) aufweist, wobei n 2 ist und R^2 Methyl darstellt.

5. Verbindung nach Anspruch 1, die
endo-8-Methyl-3-(2-pyrimidyloxy)-9-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(2-chinolyloxy)-8-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(2-pyrazinyloxy)-8-azabicyclo[3,2,1]octan,
endo-3-(6-Chlorpyridazin-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(6-Chlorpyrazin-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(Benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(Pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
2-Chinolinyl-3-chinuclidinylether,
endo-(Phenanthrin-6-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(3-methyl-5,6-cyclohexenopyridin-2-yloxy)-8-azabicyclo[3,2,1]octan,
endo-2-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cycloheptenopyridin-3-carbonsäre-ethylester
oder ein pharmazeutisch annehmbares Salz hievon ist.

6. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, das umfaßt:
(a) das Kondensieren einer Verbindung der Formel

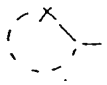


(VI)

oder eines N-Oxids hievon mit einer Verbindung der Formel

Z^1 - B (VII),

worin



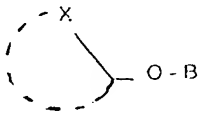
und B wie in Anspruch 1 definiert sind und eines von Z und Z^1 Hydroxy und das andere eine Abgangsgruppe ist, oder
(b) das Ersetzen oder Entfernen eines Substituenten an der Heteroarylgruppe oder des azabicyclischen Ringes einer Verbindung der Formel (I) durch bekannte Verfahren, wobei eine andere Verbindung der Formel (I) erhalten wird, oder
(c) das Oxidieren einer Verbindung der Formel (I) zum heteroaromatischen N-Oxid hievon oder
(d) das Überführen einer Verbindung der Formel (I) oder des heteroaromatischen N-Oxids hievon in das pharmazeutisch annehmbare Säureadditionssalz hievon.

7. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der Ansprüche 1 bis 5 in Verbindung mit einem pharmazeutisch annehmbaren Träger umfaßt.

8. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung als Pharmazeutikum.

Patentansprüche für folgende Vertragsstaaten : ES, GR

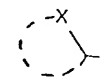
1. Verfahren zum Herstellen einer Verbindung der allgemeinen Formel (I)



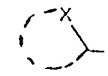
(I),

worin

eine Heteroarylgruppe mit mindestens einem Heteroatom X ausgewählt aus der Gruppe bestehend aus Stickstoff, Sauerstoff und Schwefel und gegebenenfalls substituiert durch eine oder mehrere Gruppen ausgewählt aus C_1-C_4-Alkyl, C_1-C_4-Alkoxy, Amino, C_1-C_4-Alkylamino, Di(C_1-C_4-alkylamino), Halogen, Trifluormethyl, Phenyl, Halogenphenyl, C_1-C_4-Alkylphenyl, C_1-C_4-Alkoxyphenyl, Carboxy, Carboxamido, Nitro, Thiol, C_1-C_4-Alkylthio und C_1-C_4-Alkoxycarbonyl ist; -B einen gesättigten azabicyclischen Ring mit 7 bis 11 Ringkohlenstoffatomen und einem Ringstickstoffatom, das vom O-Atom der Etherbindung durch 2 oder 3 Ringkohlenstoffatome getrennt ist, und, wenn das Ringstickstoffatom nicht in der Brückenkopfstellung ist, das N unsubstituiert oder durch eine Gruppe R^1 substituiert sein kann, wobei R^1 C_1-C_6-Alkyl, C_3-C_5-Alkenyl, C_3-C_6-Cycloalkyl, C_3-C_6-Cycloalkyl-C_1-C_2-alkyl oder Aryl- oder Heteroaryl-C_1-C_2-alkyl ist (wobei die Arylgruppe ein Phenyl- oder Naphthylrest ist, der gegebenenfalls ein- oder mehrfach durch Halogen, C_1-C_4-Alkoxy oder C_1-C_4-Alkyl substituiert ist, und die Heteroarylgruppe ein mono- oder bicyclischer Heteroarylrest mit einem oder zwei Heteroatomen ausgewählt aus Sauerstoff, Stickstoff und Schwefel ist), und die Gruppe -OB ortho zum Heteroatom X ist; mit der Maßgabe, daß



von einem substituierten oder unsubstituierten Isochinolinylrest verschieden ist und daß, wenn B einen Chinuclidyl- oder Tropanylrest darstellt,



von einem substituierten oder unsubstituierten 2-Pyridylrest verschieden ist, oder eines heteroaromatischen N-Oxids der Verbindung, worin X Stickstoff ist, oder eines pharmazeutisch annehmbaren Säureadditionssalzes der Verbindung der Formel (I) oder des N-Oxids, das umfaßt:

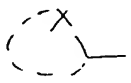
(a) das Kondensieren einer Verbindung der Formel

(VI)

oder eines N-Oxids hievon mit einer Verbindung der Formel

Z^1 - B (VII),

worin



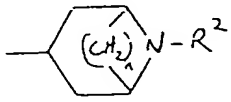
und B wie oben definiert sind und eines von Z und Z^1 Hydroxy und das andere eine Abgangsgruppe ist, oder
(b) das Ersetzen oder Entfernen eines Substituenten an der Heteroarylgruppe oder des azabicyclischen Ringes einer Verbindung der Formel (I) durch bekannte Verfahren, wobei eine andere Verbindung der Formel (I) erhalten wird, oder
(c) das Oxidieren einer Verbindung der Formel (I) zum heteroaromatischen N-Oxid hievon oder
(d) das Überführen einer Verbindung der Formel (I) oder des heteroaromatischen N-Oxids hievon in das pharmazeutisch annehmbare Säureadditionssalz hievon.

2. Verfahren nach Anspruch 1, das das Kondensieren einer Verbindung der Formel (VI), worin Z Halogen ist, mit einer Verbindung der Formel (VII), worin Z^1 Hydroxy darstellt, umfaßt.

3. Verfahren nach Anspruch 1 oder 2, wobei im Produkt

2-Pyridyl gegebenenfalls substituiert durch Chlor, Nitro, C_1-C_4-Alkyl oder Carboxamido; 2- oder 4-Pyrimidyl gegebenenfalls substituiert durch Chlor, Amino, C_1-C_4-Alkoxy; 2-Pyrazinyl gegebenenfalls substituiert durch Halogen oder C_1-C_4-Alkyl; 2-Pyridazinyl gegebenenfalls substituiert durch Halogen oder C_1-C_4-Alkoxy; 2-Chinolyl gegebenenfalls substituiert durch C_1-C_4-Alkyl; 2-Thienyl; 2-Benzo(b)-thienyl; 1H-Indazol-3-yl gegebenenfalls substituiert durch Nitro oder C_1-C_4-Alkyl; 2-Benzoxazolyl; 2-Benzothiazolyl und 6-Phenanthrinyl ist.

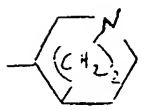
4. Verfahren nach einem der Ansprüche 1 bis 3, wobei im Produkt B
(a)



(II),

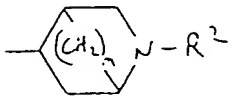
worin n 2, 3 oder 4 ist und R^2 Wasserstoff ist oder die für R^1 in Anspruch 1 angegebene Bedeutung hat,

(b)



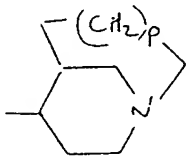
(III),

(c)



(IV),

worin R^2 die oben angegebene Bedeutung hat und m 1, 2 oder 3 ist, oder
(d)



(V),

worin p Null, 1 oder 2 ist, darstellt.

5. Verfahren nach Anspruch 4, wobei B die Formel (II) aufweist, in der n 2 ist und R^2 Methyl darstellt.

6. Verfahren nach Anspruch 1, bei dem das Produkt
endo-8-Methyl-3-(2-pyrimidyloxy)-8-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(2-chinolyloxy)-8-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(2-pyrazinyloxy)-8-azabicyclo[3,2,1]octan,
endo-3-(6-Chlorpyridazin-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(6-Chlorpyrazin-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(Benzothiazol-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(Pyridazin-3-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
2-Chinolinyl-3-chinuclidinylether,
endo-(Phenanthrin-6-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-3-(Benzoxazol-2-yloxy)-8-methyl-8-azabicyclo[3,2,1]octan,
endo-8-Methyl-3-(3-methyl-5,6-cyclohexenopyridin-2-yloxy)-8-azabicyclo[3,2,1]octan,
endo-2-(8-Methyl-8-azabicyclo[3,2,1]octan-3-yloxy)-5,6-cycloheptenopyridin-3-carbonsäure-ethylester
oder ein pharmazeutisch annehmbares Salz hievon ist.

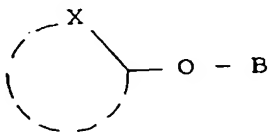
7. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung, das das Vereinigen einer Verbindung der allgemeinen Formel (I), wie in Anspruch 1 definiert, oder eines heteroaromatischen N-Oxids der Verbindung, worin X Stickstoff ist, oder eines pharmazeutisch annehmbaren Säureadditionssalzes der Verbindung der Formel (I) oder des N-Oxids mit einem pharmazeutisch annehmbaren Träger umfaßt.

8. Verfahren nach Anspruch 7, in dem der aktive Bestandteil nach dem in einem der Ansprüche 1 bis 6 beanspruchten Verfahren hergestellt ist.

Revendications

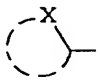
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Composé de formule générale (I) :



(I)

où



représente un radical hétéroaryle contenant au moins un hétéroatome X choisi dans la classe formée par l'azote, l'oxygène et le soufre et étant facultativement substitué par un ou plusieurs radicaux choisis parmi C_{1-4}-alcoyle, C_{1-4}-alcoxy, amino, C_{1-4}-alcoylamino di(C_{1-4}-alcoyl)amino, halogène, trifluorométhyle, phényle, halophényle, C_{1-4}-alcoylphényle, C_{1-4}-alcoxyphényle, carboxyle, carboxamido, nitro, thiol, C_{1-4}-alcoylthio et C_{1-4}-alcoxycarbonyle; B représente un cycle azabicyclique saturé comprenant 7 à 11 atomes de carbone de cycle et un atome d'azote de cycle qui est séparé de l'atome O de la liaison éther par deux ou trois atomes de carbone de cycle et lorsque l'atome d'azote de cycle n'est pas en position de tête de pont, le N peut être non substitué ou substitué par un radical R^1 où R^1 est C_{1-6}-alcoyle, C_{3-5}-alcényle, C_{3-6}-cycloalcoyle, C_{3-6}-cycloalcoyl-C_{1-2}-alcoyle ou aryl- ou hétéroaryl-C_{1-2}-alcoyle (où le radical aryle est un radical phényle ou naphtyle facultativement substitué par un ou plusieurs radicaux halogène, C_{1-4}-alcoxy ou C_{1-4}-alcoyle et le radical hétéroaryle est un radical hétéroaryle mono- ou bicyclique contenant un ou deux hétéroatomes choisis parmi oxygène, azote et soufre) et la partie -OB occupe la position ortho par rapport à l'hétéroatome X; avec la restriction que

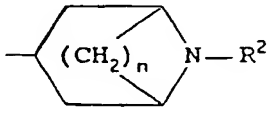
est autre qu'un radical isoquinolinyle substitué ou non substitué et que lorsque B représente un radical quinuclidyle ou tropannyle,

est autre qu'un radical 2-pyridyle substitué ou non substitué;
ou un N-oxyde hétéroaromatique du composé où X est azote; ou un sel d'addition d'acide pharmaceutiquement acceptable du composé de formule I ou du N-oxyde.

2. Composé suivant la revendication 1, où

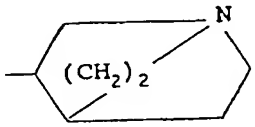
est 2-pyridyle facultativement substitué par chloro, nitro, C_{1-4}-alcoyle ou carboxamido, 2- ou 4-pyrimidyle facultativement substitué par chloro, amino, C_{1-4}-alcoxy; 2-pyrazinyle facultativement substitué par halo ou C_{1-4}-alcoyle; 2-pyridazinyle facultativement substitué par halo ou C_{1-4}-alcoxy; 2-quinolyle facultativement substitué par C_{1-4}-alcoyle; 2-thiényle; 2-benzo(b)thiényle; 1H-indazol-3-yle facultativement substitué par nitro ou C_{1-4}-alcoyle; 2-benzoxazolyle; 2-benzothiazolyle; ou 6-phénanthrinyle.

3. Composé suivant la revendication 1 ou 2, dans laquelle B est :
(a)



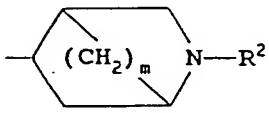
(II)

où n est 2, 3 ou 4 et R^2 est hydrogène ou a la signification attribuée à R^1 dans la revendication 1,
(b)



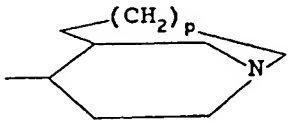
(III)

(c)



(IV)

où R^2 a la signification attribuée ci-dessus et m est 1, 2 ou 3 ou
(d)



(V)

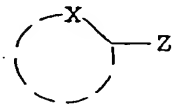
où p est 0, 1 ou 2.

4. Composé suivant la revendication 3, dans lequel a est de formule (II) où n est 2 et R^2 est méthyle.

5. Composé suivant la revendication 1 qui est
l'endo-8-méthyl-3-(2-pyrimidyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(2-quinolyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(2-pyrazinyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(6-chloropyridazin-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane

ou
l'endo-3-(6-chloropyrazin-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(benzothiazol-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(pyridazin-3-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'éther 2-quinolinyl-3-quinuclidinylique
ou
l'endo-(phénanthrin-6-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(benzoxazol-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(3-méthyl-5,6-cyclohexénopyridin-2-yloxy)-8-azabicyclo[3.2.1]octane
ou
l'ester éthylique de l'acide endo-2-(8-méthyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cyclohepténopyridine-3-carboxylique
ou un sel pharmaceutiquement acceptable de l'un de ceux-ci.

6. Procédé de préparation d'un composé suivant la revendication 1, qui comprend :
(a) la condensation d'un composé de formule

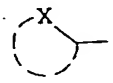


(VI)

ou d'un N-oxyde de celui-ci, avec un composé de formule

Z^1-B (VII)

où



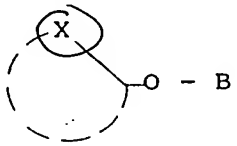
et B sont tels que définis dans la revendication 1 et l'un d'entre Z et Z^1 est hydroxyle et l'autre est un radical partant, ou
(b) le remplacement ou l'élimination d'un substituant sur le radical hétéroaryle ou le cycle azabicyclique d'un composé de formule (I) par des procédés connus dans la spécialité pour former un autre composé de formule I, ou
(c) l'oxydation d'un composé de formule (I) en le N-oxyde hétéroaromatique de celui-ci, ou
(d) la conversion d'un composé de formule (I) ou du N-oxyde hétéroaromatique de celui-ci en son sel d'addition d'acide pharmaceutiquement acceptable.

7. Composition pharmaceutique contenant un composé suivant l'une quelconque revendications 1 à 5 en association avec un excipient pharmaceutiquement acceptable.

8. Composé suivant l'une quelconque des revendications 1 à 5 à utiliser comme agent pharmaceutique.

Revendications pour les Etats contractants suivants : ES, GR

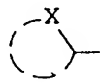
1. Procédé de préparation d'un composé de formule générale (I) :



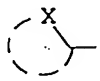
(I)

où

représente un radical hétéroaryle contenant au moins un hétéroatome X choisi dans la classe formée par l'azote, l'oxygène et le soufre et étant facultativement substitué par un ou plusieurs radicaux choisis parmi C_{1-4}-alcoyle, C_{1-4}-alcoxy, amino, C_{1-4}-alcoylamino, di(C_{1-4}-alcoyl)amino, halogène, trifluorométhyle, phényle, halophényle, C_{1-4}-alcoylphényle, C_{1-4}-alcoxyphényle, carboxyle, carboxamido, nitro, thiol, C_{1-4}-alcoylthio et C_{1-4}-alcoxycarbonyle; B représente un cycle azabicyclique saturé comprenant 7 à 11 atomes de carbone de cycle et un atome d'azote de cycle qui est séparé de l'atome O de la liaison éther par deux ou trois atomes de carbone de cycle et lorsque l'atome d'azote de cycle n'est pas en position de tête de pont, le N peut être non substitué ou substitué par un radical R^1 où R^1 est C_{1-6}-alcoyle, C_{3-5}-alcényle, C_{3-6}-cycloalcoyle, C_{3-6}-cycloalcoyl-C_{1-2}-alcoyle ou aryl- ou hétéroaryl-C_{1-2}-alcoyle (où le radical aryle est un radical phényle ou naphtyle facultativement substitué par un ou plusieurs radicaux halogène, C_{1-4}-alcoxy ou C_{1-4}-alcoyle et le radical hétéroaryle est un radical hétéroaryle mono- ou bicyclique contenant un ou deux hétéroatomes choisis parmi oxygène, azote et soufre) et la partie -OB occupe la position ortho par rapport à l'hétéroatome X; avec la restriction que

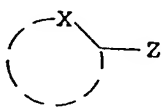


est autre qu'un radical isoquinolinyle substitué ou non substitué et que lorsque B représente un radical quinuclidyle ou tropannyle,



est autre qu'un radical 2-pyridyle substitué ou non substitué;
ou d'un N-oxyde hétéroaromatique du composé où X est azote;
ou d'un sel d'addition d'acide pharmaceutiquement acceptable du composé de formule I ou du N-oxyde.
qui comprend :

(a) la condensation d'un composé de formule

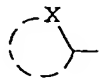


(VI)

ou d'un N-oxyde de celui-ci, avec un composé de formule

Z^1-B (VII)

où



et B sont tels que définis ci-dessus et l'un d'entre Z et Z^1 est hydroxyle et l'autre est un radical partant, ou

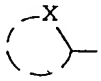
(b) le remplacement ou l'élimination d'un substituant sur le radical hétéroaryle ou le cycle azabicyclique d'un composé de formule (I) par des procédés connus dans la spécialité pour former un autre composé de formule I, ou

(c) l'oxydation d'un composé de formule (I) en le N-oxyde hétéroaromatique de celui-ci, ou

(d) la conversion d'un composé de formule (I) ou du N-oxyde hétéroaromatique de celui-ci en son sel d'addition d'acide pharmaceutiquement acceptable.

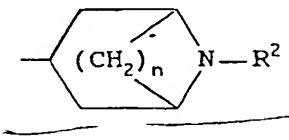
2. Procédé suivant la revendication 1, qui comprend la condensation d'un procédé de formule (VI) où Z est halogène avec un composé de formule (VII) où Z^1 est hydroxyle.

3. Procédé suivant la revendication 1 ou 2, dans lequel dans le produit,



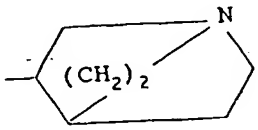
est 2-pyridyle facultativement substitué par chloro, nitro, C_{1-4}-alcoyle ou carboxamido, 2- ou 4-pyrimidyle facultativement substitué par chloro, amino, C_{1-4}-alcoxy; 2-pyrazinyle facultativement substitué par halo ou C_{1-4}-alcoyle; 2-pyridazinyle facultativement substitué par halo ou C_{1-4}-alcoxy; 2-quinolyle facultativement substitué par C_{1-4}-alcoyle; 2-thiényle; 2-benzo(b)thiényle; 1H-indazol-3-yle facultativement substitué par nitro ou C_{1-4}-alcoyle; 2-benzoxazolyle; 2-benzothiazolyle; ou 6-phénanthrinyle.

4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel dans le produit B est :
(a)



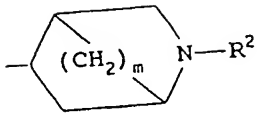
(II)

où n est 2, 3 ou 4 et R^2 est hydrogène ou a la signification attribuée à R^1 dans la revendication 1,
(b)



(III)

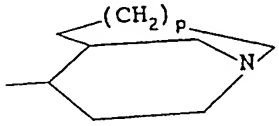
(c)



(IV)

où R^2 a la signification attribuée ci-dessus et m est 1, 2 ou 3, ou

(d)



(V)

où p est 0, 1 ou 2.

5. Procédé suivant la revendication 4, dans lequel B est de formule (II) où n est 2 et R^2 est méthyle.

6. Procédé suivant la revendication 1, dans lequel le produit est l'endo-8-méthyl-3-(2-pyrimidyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(2-quinolyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(2-pyrazinyloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(6-chloropyridazin-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(6-chloropyrazin-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(benzothiazol-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(pyridazin-3-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'éther 2-quinolinyl-3-quinuclidinylique
ou
l'endo-(phénanthrin-6-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-3-(benzoxazol-2-yloxy)-8-méthyl-8-azabicyclo[3.2.1]octane
ou
l'endo-8-méthyl-3-(3-méthyl-5,6-cyclohexénopyridin-2-yloxy)-8-azabicyclo[3.2.1]octane
ou
l'endo-2-(8-méthyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5,6-cyclohepténopyridi-
ou un sel pharmaceutiquement acceptable de l'un de ceux-ci.

7. Procédé de préparation d'une composition pharmaceutique, qui comprend la mise en association d'un composé de formule générale (I) tel que défini dans la revendication 1 ou d'un N-oxyde hétéroaromatique du composé où X est azote ou d'un sel d'addition d'acide pharmaceutiquement acceptable du composé de formule (I) ou du N-oxyde, avec un excipient pharmaceutiquement acceptable.

8. Procédé suivant la revendication 7 dans lequel le constituant actif est préparé par le procédé suivant l'une quelconque des revendications 1 à 6.